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Medical research

Immune features linked to COVID susceptibility

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Controlled infection with SARS-CoV-2 of people who hadn't previously been exposed to the virus reveals how molecular and cellular signatures of the immune response portend effective defence against COVID-19.

More than four years after the start of the COVID-19 pandemic, and the mass mobilization of the scientific community, key questions remain about why some people get infected and others don't. What early immune responses are required to control infection, and which responses are associated with uncontrolled infection and disease? Writing in *Nature*, Lindeboom *et al.*[1] tackle these queries head-on, using a controlled human infection model in which unvaccinated individuals who hadn't previously encountered the SARS-CoV-2 virus were exposed to it. This work provides unprecedented insights into the dynamics of immune responses to exposure of the virus.

The study addresses the long-standing puzzle of divergent infection outcomes among individuals exposed to the same amount (dose) of virus. Although factors such as proximity to infected individuals and duration of exposure are known to influence whether a person gets infected, the role of immunological factors that control the development of infection remains poorly understood. Until now, it has been very difficult to assess the extremely early immunological responses or the pre-infection immunological states that are associated with protection from infection. Using a controlled human infection model, Lindeboom and colleagues overcome this challenge, grasping a unique opportunity to investigate immunological responses pre- and post-infection.

In this study, 16 young healthy adults, who were unvaccinated against COVID-19 and did not have signs of previous infection in terms of antibodies against SARS-COV-2 proteins, were inoculated nasally with an extremely low dose of the original strain of SARS-CoV-2. In-depth single-cell profiling of gene expression was done using paired samples of nasal swabs (samples of nasopharyngeal mucosal tissue) and blood cells from each individual before infection. Samples were then taken periodically after infection for up to 28 days. Six out of the sixteen participants developed sustained infection (associated with mild symptoms) characterized by persistent positive viral testing on multiple tests. Interestingly, of the ten people who did not develop a sustained infection, three of these developed a 'transient' infection characterized by intermittent positive viral testing of nasal swabs, and seven developed an 'abortive' infection characterized by no positive results when testing for viral presence.

Notably, despite differences in their infection outcomes, participants across all groups shared similar early gene-expression signatures of activation of the innate branch of the immune response, including a transient loss of the activated version of immune cells called monocytes and a rise in the level in the blood of activated mucosal-associated invariant T cells — immune cells associated with innate defences. These findings suggest a common response to viral exposure, shedding light on previously unidentified aspects of the innate immune response. Whether these changes are observed with other types of viral exposure in the respiratory passageways remains to be explored.

Distinct patterns emerge when comparing sustained and transient infections (Fig. 1). Transiently infected participants have a robust type of antiviral defence response termed a

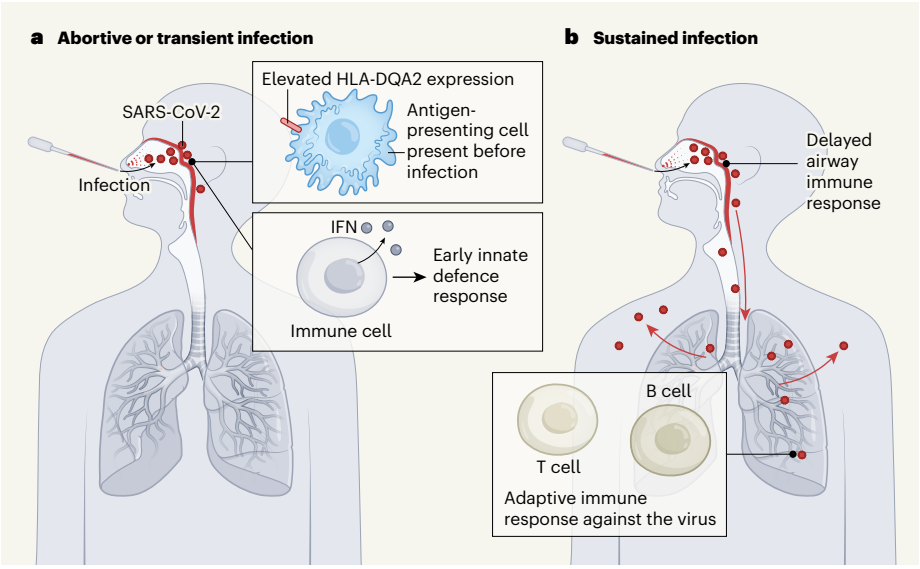

Figure 1 | Immune responses in the context of SARS-CoV-2 infection. Lindeboom *et al.*[1] report a controlled human infection model in which individuals who hadn't previously encountered the SARS-CoV-2 virus were exposed to it for the first time. Their immune-system defences were assessed before and after infection by examining gene expression of cells obtained from nasal swabs or blood samples. **a**, Elevated levels of the protein HLA-DQA2 in immune cells called antigen-presenting cells before infection were associated with either abortive infection (no signs of viral presence in testing) or transient infection (intermittent positive results for viral presence in testing). Early defence responses associated with the protein interferon (IFN), called type I interferon (IFN-I) responses, observed in cells (including immune cells) of the upper airway, were associated only with transient infection. **b**, Participants who had delayed IFN-I responses in the upper airway developed a persistent infection, which induced B- and T-cell responses of the adaptive branch of the immune system.

type I interferon (IFN-I) response in the nasal mucosal tissue shortly after viral exposure (day 1 after infection), potentially contributing to viral removal. By contrast, participants who had sustained infection showed delayed (only starting on day 5 after infection) mucosal IFN-I responses, as well as delays in immune-cell infiltration into the nasopharynx, indicating an impaired innate antiviral response at the site of initial viral inoculation and replication.

Why some individuals can develop early mucosal IFN-I responses and others cannot remains an important question to answer. These observations are consistent with previous reports that link deficiencies in interferon signalling to increased susceptibility to SARS-CoV-2 infection[2,3]. Notably, the timing of interferon responses suggests a window of opportunity for therapeutic intervention, highlighting the potential effectiveness of IFN-I-inducing therapies administered to nasal mucosal tissues either before exposure or within the first 24 hours of infection. This might explain why there have been mixed results from clinical trials investigating IFN-I-based therapeutics[4–6].

The only IFN-I response observed in the blood was found in cases of sustained infection, occurring at day 3 after infection. Notably, this was earlier than the response was observed in the nasopharynx of these participants. The IFN-I signature in blood samples might represent the early movement of immune cells from the site of infection. This finding is consistent with another key observation of this study: that only sustained infection resulted in the induction of responses to SARS-CoV-2 from the adaptive branch of the immune system (mobilization of immune cells called T cells and B cells). This highlights the idea that reaching a threshold of infection or viral replication is required for the engagement of adaptive immunity and memory responses.

The study identifies a pre-exposure immune signature associated with protection from sustained infection. The authors found higher levels of the messenger RNA that encodes the protein HLA-DQA2 in multiple lineages of immune cells called antigen-presenting cells, both in the nasal mucosa and in blood in people who had transient or abortive infections. HLA-DQA2 mRNA levels were elevated before viral exposure and maintained after viral exposure (Fig. 1). HLA-DQA2 is a type of protein known as an MHC class II molecule, and these are typically involved in presenting foreign protein fragments (antigens) to immune cells called $CD4^+$ T cells to initiate adaptive immune responses. Interestingly, previous single-cell gene-expression studies identified lower expression of HLA-DQA2 as being associated with increased disease severity of COVID-19 (refs 7, 8).

However, unlike regular MHC II molecules, HLA-DQA2 does not seem to perform typical antigen-presenting functions[9]. Although exactly how HLA-DQA2 expression confers antiviral activities remains unclear, versions of genes that encode HLA-DQA2 were previously identified as being associated with certain autoimmune diseases, such as type 1 diabetes[10], rheumatoid arthritis[11] and Parkinson's disease[12]. By identifying the pre-exposure protective effect of HLA-DQA2 expression, this study suggests a non-typical role of this MHC II molecule in innate resistance to SARS-CoV-2 infection.

The authors leverage the unique time-resolved single-cell gene-expression data of this study to build a dynamic reference atlas of the cells and molecules mobilized during early stages of COVID-19 in people, providing a valuable resource for the scientific community. Although the ethical considerations of this SARS-CoV-2 controlled human infection model have been discussed elsewhere (see go.nature.com/45q0q9o), it should be noted that participants in this study only experienced mild symptoms and no participant was reported to have developed long COVID. Controlled human infection models have long provided valuable information about human immunity and protection in relation to disease-causing agents, and future plans with this model include testing intranasal vaccine candidates (see go.nature.com/3yv2xmt).

Lindeboom and colleagues' study is a notable step forward in understanding the complexities of SARS-CoV-2 infection. By unravelling the mysteries of early immune responses, the study offers promising avenues for future research and therapeutic development in the ongoing fight against COVID-19.

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